REMARKS

Claims 1-9 and 11 have been amended to a form more consistent with U.S. practice. New claims 13 and 14 have been introduced into the application. No additional fee is due. Support for claims 13 and 14 can be found in the specification on page 10. The Examiner should note that claim 10 was cancelled by way of a preliminary amendment.

Submitted herewith is a substitute specification which conforms with that which was originally filed in the U.S. Patent and Trademark Office.

The present invention is in a pharmaceutical formulation. Prior to the present invention, the preferred method of production of microcapsules was by spray drying from a solution. However that method would not produce a coated powder having sustained release properties. While not wishing to be bound by theory the traditional teaching is that sustained release properties could not be obtained because the coating was too porous. The speculation was that the porous coating resulted because of the formation of blow holes in the final coating. Such blow holes were not necessarily deleterious to the taste masking properties of the coating since the rate of diffusion of active compound through these blow holes need not be fast enough to be noticeable given the short residence time of the powder in the mouth during consumption. However, such a blow hole compromises the sustained release properties of the powder thus formed due to the significantly longer residence times in the stomach. Therefore, the traditional teaching was that a spray drying processes will not produce a particle having adequate taste masking and sustained release properties. See the article by Deasy (1994) in Microencapsulation and Related Drug Processes, chapter 8:pp 181 -192 Marcel Dekker, Inc. referred to in the specification at page 1, lines 22-27.

In contrast to that teaching, Applicants have overcome these problems as evidenced by the bioavailability study shown in Table 2 which demonstrates that the powders of the present invention provide sustained release properties when compared to non-coated products. Accordingly the applicants present invention provides a significant improvement over the prior art.

Claims 1-8 and 11 have been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,767,789 to Blank et al. ("Blank"). It is submitted this rejection is improper and should be withdrawn.

For a single reference to anticipate a claimed invention, that reference must show each and every feature of the claimed invention and those features must be arranged as in the claimed invention. Thus, Blank is not an anticipatory reference as a matter of law. See Connell v. Sears Roebuck & Co., 220 U.S.P.Q. 193 (Fed. Cir. 1983). Thus, it is submitted the rejection under 35 U.S.C. § 102 is in error as a matter of law.

Blank is directed to an immediate release taste masked spray dried product. In col. 1 Blank states "this invention relates to a novel therapeutic form of spray dried acetaminophen having a neutral taste which can be formulated into for example, fast dissolving dosage forms as described in U.S. Pat. Nos. 4,3O5,5O2 and 4,371,516. Those latter references describe " the fast dissolving dosage forms" which "disintegrate in water within five seconds or less and hence dissolve rapidly in the saliva of the mouth". See col. 1, lines 33-36. Thus, assuming Blank's spray dried powders had taste masking properties, there is no teaching or suggestion that Blank's product had sustained release properties. Indeed, the strong suggestion of the reference is that Blank's products are immediate release type products. In

contrast, the present invention is in a spray dried product which is both sustained release and taste masking.

There is no suggestion in Blank that sustained release properties can be obtained using the spray drying techniques described therein. As discussed above, one skilled in the art on reading Blank in light of the teaching of the Deasy review would not consider Blank to disclose a sustained release formulation nor is there any teaching or suggestion that this is achieved. As discussed previously, while taste masking is an important objective possibly addressed by Blank, the present invention also provides the additional important feature in that the powders thus produced have sustained release properties as evidenced by the data set forth in the examples of the present application.

Applicants respectfully submit that the teachings of Blank do not disclose or anticipate the presently claimed invention which requires that the powder be both taste masked and have sustained release properties.

Furthermore, the rejection of claims 2 to 5 and 7 is also in error. There is no disclosure of the subject matter of these claims in Blank. There is no teaching in Blank of the particle size of the core (claims 2 and 3), nor a teaching of the thickness of the coating provided therein. Furthermore, especially in relation to claims 4 and 5, there is a positive teaching in Blank that the weight percentage of the coating must be in the range of 24 to 40 wt.~% for effective taste masking. It is erroneous to maintain that Blank discloses the subject matter of claims 4 and 5 which relate to coating amounts of less than 23 wt.~% of the formulation and 20% wt.~% of the formulation respectively. Blank not only fails to disclose coating amounts within these ranges but indeed contains a positive teaching away from such ranges at col. 2 lines

3-8. Accordingly, it is respectfully submitted that there can be no anticipation of those claims by Blank.

Claims 1-8 and 11 have been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,354,566 to Sparks et al. ("Sparks"). It is submitted the rejection is improper and should be withdrawn.

The Examiner maintains that Sparks discloses controlled release taste masked particles comprising either antibiotics such as erythromycin or analgesics such as acetaminophen coated with a polymer such as ethyl cellulose. However, the particles disclosed in the Sparks reference and those disclosed in the present application are fundamentally different. According to Sparks,

> The microparticles according to the invention are to be distinguished from microcapsules in that in the latter the active ingredient is encapsulated by a polymer coating, whereas in the former the active ingredient is uniformly distributed throughout the polymeric material as described above and as illustrated in FIGS 1 and 2 of the accompanying drawings.

See col. 9, line 64 to col. 10, line 2.

Therefore, Sparks is not directed to microcapsules as is the present invention but is referring to microparticles distributed throughout a matrix. At col. 9, line 25, Sparks states "each of the particles of the controlled release powder according to the invention represents a true micromatrix with the active ingredient and optionally one or more excipients uniformly distributed therethrough as depicted in FIG. 1" (underlining added). Sparks continues at line 33, "the theophylline can be observed to form veins or a labyrinth throughout the polymeric material of the pharmasomes".

It is apparent from Figs. 1 and 2 that the active ingredient is uniformly distributed throughout the matrix. Fig. 1 illustrates the active ingredient forming veins throughout the polymeric material. Fig. 2 clearly shows the veins or dark portions after the active ingredient has been leached out. Additionally, the Examiner's attention is invited to col. 22, line 14 which states "each of said microparticles being in the form of a micromatrix with the active ingredient uniformly distributed therethrough but not entirely coated by polymer". Thus, Sparks is clearly directed to a microparticle in which the active ingredient is uniformly distributed throughout the particle and in which the particle does not have a continuous coating on the outside. See Sparks claim 1.

In contrast, the present invention requires a core element and a coating. Sparks at col. 9 implicitly indicates that this is different from his invention.

Further, in the now claimed invention there is a "substantially continuous polymer coating thereon". Accordingly, the present invention requires the spray dried powder particles to contain a substantially continuous polymer coating on the outside. This is in contrast to Sparks which specifically teaches that the microparticles must not have a substantially continuous coating on the outside. Thus, there is no disclosure or suggestion by Sparks of the now claimed subject matter.

It is further submitted that Sparks at col. 6, lines 29-32 is not an enabling disclosure as to spray drying since all of Sparks examples refer to the use of a rotary evaporator and there is no disclosure that the particles produced in Sparks could indeed be prepared by spray drying. Accordingly, it is submitted that there is no enabling disclosure in Sparks of the now claimed subject matter.

The Examiner states that Sparks' product achieves the desired results of controlled release and taste masking and the coating thickness should not be given patentable weight. As discussed above, the Examiner's conclusion is in error.

Claim 9 has been rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,808,411 to Lu et al. ("Lu"). The Examiner states that Lu discloses a dried particle composition containing clarithromycin which is optionally coated with ethyl cellulose. It is submitted the rejection is improper and should be withdrawn.

Claim 9 depends from claim 1 and therefore incorporates all the limitations of claim 1. An important feature of claim 1 is that the particles are produced by a spray drying process to produce a substantially continuous polymeric coating on the outside of the core element which contains one or more pharmaceutically active compounds. There is no disclosure in Lu of the use of spray drying to produce the product. Lu refers to a fluid bed process which is significantly different and leads to a product with a different property than the microcapsules of the present application.

The Examiner's attention is invited to col. 3, lines 45-64 of Lu which indicates that the products referred to therein are reaction products (or complexes) between the active drug and the polymer. This material or reaction product is Glatt or suspension coated which is different from the present invention. Lu's process of manufacture is different as is the relationship between the active agents and the coating polymer. Accordingly, it is submitted there is no disclosure or suggestion of the present invention in Lu.

Claims 1-8, 10 and 11 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Blank in view of U.S. Patent No. 5,378,474 to Morella et al. ("Morella"). It is submitted this rejection is also improper and should be withdrawn.

Blank has been discussed above.

A spray drying process as described in Blank typically begins with a mixture of solid active compound, a solvent, and a coating material which is soluble in the solvent. Additional additives can be used which are either soluble or insoluble in the solvent in the spray drying process. The material is then transported to the spray dryer in which evaporation of the solvent occurs. This leads to an increase in concentration of the dissolved components in the solvent resulting in their coming out of solution and coating the insoluble particles. Accordingly, when the spray drying process is used it is typical that the insoluble components will end up being coated by the dissolved components. The insoluble components therefore will normally end up in the core of the material produced.

One of ordinary skill in the art would not be motivated to combine the teachings of Morella with the teachings of Blank. Blank is directed towards a spray drying process whereas the Morella coating process is not spray drying but instead relates to a fluid bed process. See col. 15, lines 40-50 which state that Morella is directed to the production of pellets. One of ordinary skill in the art would understand that fluid bed processes and spray dryer processes are significantly different coating processes leading to significantly different products being produced and that the teachings from one process of making coated particles can not necessarily be carried over into a teaching of another production technique. Morella relates to a sustained release pharmaceutical composition of three components as follows:

1. at least one polymer which is substantially insoluble independent of pH (insoluble matrix polymer)
2. at least one enteric polymer which is substantially insoluble at acidic pH but at least partially soluble at a less acid to basic pH (enteric polymer): and

3. at least one component which is at least partially soluble at acidic pH (acid soluble polymer).

Morella provides a positive teaching starting at col. 8, line 46 that "it has been found necessary in order to achieve a slow rate of release at acidic pH for pH dependent or independent drugs. and faster relatively constant rate of release over an extended period of time to include the above three components in the hybrid core coating composition".

One of ordinary skill in the art would therefore understand from the teachings of Morella that in order to achieve sustained release that these three components are necessary, not merely optional. The skilled art worker would understand however that the coatings referred to by Morella include solid components (as one of the components is insoluble). One of ordinary skill would therefore understand that if such a component were used in a spray drying approach as described in Blank the solid components would end up in the core of the particle and not in the coating. The result promised by Morella would therefore not be achieved. One of ordinary skill would understand that the teachings in Morella are limited to batch granulation or fluid bed type processes in which the solid core is preformed and is then coated. A process such as a spray drying process wherein the solid core is not preformed would not be amenable to modification by the teachings of Morella. Accordingly, Applicants must respectfully disagree with the Examiner's position that one of ordinary skill would be motivated to coat the formulation of Blank according to the coating amount and thickness from Morella with a reasonable expectation of obtaining a pharmaceutical composition that has good taste masking properties and provides sustained release.

Claim 9 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Blank in view of U.S. Patent No. 5,707,646 to Yajima et al. ("Yajima"). It is submitted this rejection is improper and should be withdrawn.

Blank has been discussed above.

As discussed above, Blank is silent as to a salient feature of the invention that the composition has a sustained release profile. Indeed, Yajima is also wholly silent on this point. Even if one of ordinary skill were to combine the two references, there is no teaching of the sustained release profile recited in claim 9. Thus it can not have been obvious to one skilled in the art at the time of the invention to make a formulation as taught by Blank containing the clarithromycin of Yajima with a reasonable expectation of producing a pharmaceutical powder within the scope of the present invention.

Claim 9 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Sparks in view of Lu. It is submitted this rejection is improper and should be withdrawn.

Both Sparks and Lu have been discussed above.

Sparks does not disclose microcapsules as required by the present invention. A salient difference between Sparks and the present invention is that in Sparks the active is randomly dispersed through the micromatrix and, furthermore, there is a positive teaching in Sparks that the coating is not continuous. In contrast, the present invention requires a continuous coating of the polymeric coating material on the core containing the pharmaceutical compound.

Therefore, even if one skilled in the art were to combine the teachings of Sparks with the teachings of Lu, one would not arrive at the spray dried particles of the present invention which, as recited in claim 1 are required to have "a core element of one or more

pharmaceutically active compounds and a substantially continuous polymeric coating thereon". Sparks clearly discloses that the polymeric coating should not be substantially continuous.

Therefore, were one of ordinary skill in the art to combine the teachings of any citation with the teachings of Sparks they would at best arrive at a micromatrix with the active ingredient dispersed throughout the micromaterial with the limitation that the materials do not contain a substantially continuous coating thereon. Accordingly, as claim 9 of the present application includes all the features of claim 1 it is respectfully submitted that the combination of Sparks and Lu does not render the invention of claim 9 obvious to one of ordinary skill in the art.

It is submitted that the combinations of references are improper. As discussed above, each of the references list different techniques to obtain different products with different characteristics. It is clear that the Examiner has engaged in a pick and choose technique based on hindsight using Applicants' invention as a blueprint to selectively edit the cited references. This is improper. See In re Grabiak, 226 U.S.P.Q. 870 (Fed. Cir. 1985). Further, the manner in which the Examiner has edited the references for the combination would require that salient features of the respective disclosures of the references and important features of the invention as disclosed therein be ignored. This is also improper for a rejection under 35 U.S.C. § 103. See In re Ratti, 123 U.S.P.Q. 349 (CCPA 1959).

In view of the foregoing, reconsideration and allowance of the application with claims 1-9, 11 and 13 and 14 are earnestly solicited.

With the attached Letter Transmitting Priority Documents, Applicants herewith submit certified copies of the priority documents from which priority is claimed for the above-identified application.

Respectfully submitted,

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